REMARKS

Applicant requests reconsideration of the application in view of the discussion that follows. The status of the claims as of this response is as follows: Claims 1-28 are pending. Claims 12-19 and 27-28 have been canceled herein without prejudice to Applicant's filing divisional application to the separately patentable subject matter thereof. Claims 1, 2, 5, 9 and 21 have been amended herein.

The Amendments

The specification was amended in the title and was also amended to capitalize trademarks and provide generic terminology where necessary. The Abstract of the Disclosure was amended to include other methods encompassed in the disclosure as requested in the Office Action.

Claim 1 was amended to recite that the nucleic acid sample pairs comprise different nucleic acid samples. Support therefor is in the specification, for example, page 22, lines 16-29. Claim 1 was also amended to provide proper antecedent basis and reference back to language in the claim. Support therefor is in the specification, for example, original claim 1.

Claim 2 was amended to provide proper reference back to claim 1, from which claim 2 depends. Support therefor is in the specification, for example, original claims 1 and 2.

Claim 5 was amended to correct a typographical error.

Claim 9 was amended to recite that the nucleic acid sample pairs comprise different nucleic acid samples. Support therefor is in the specification, for example, page 22, lines 16-29. Claim 9 was also amended in step (c) to recite "thereby collecting data." Support therefor is in the specification, for example, page 20, lines 23-24.

Claim 21 was amended to refer consistently to "candidate nucleic acid probe sequence." Support therefor is in the specification, for example, original claim 21.

Claim Objections

Applicant submits that the above amendments to claims 5 and 21 obviate the objection to claims 5 and 21-26 because of the presence of certain informalities.

Rejection under 35 U.S.C. §112

Claims 1-11 and 20-26 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant believes that the above amendments to the claims obviate this ground of rejection.

Rejection under 35 U.S.C. §102

Claims 1-4, and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaventure, *et al.* (Brain Research, Vol. 943, Pages 38-47, July, 2002) Bonaventure).

The Office Action contends that the above claims are drawn to a method of selecting a combination of nucleic acid sample pairs wherein the method comprises (a) conducting differential expression experiments using nucleic acid sample pairs and nucleic acid probes immobilized on a substrate and (b) selecting a nucleic acid sample pair by maximizing the number of differentially expressed genes.

Claim 1, however, is directed to a method for selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes. The method comprises (a) conducting differential expression experiments using (i) nucleic acid sample pairs wherein the pairs comprise different nucleic acid samples and (ii) nucleic acid probes immobilized on a substrate, said probes representing a set of genes where the number of genes in the set is a portion of an expected number of genes in a sample, and (b) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having (i) a maximized number of genes from the set of genes that exhibit differential expression and (ii) a minimized number of genes from the set of genes that do not exhibit differential expression.

In order to maintain a rejection under 35 U.S.C. §102(b) an examiner must first establish a *prima facie* case of anticipation. An invention is anticipated if each and every limitation of the claimed invention is disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994). It is not enough, however, that the prior art reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, anticipation requires the presence in a single prior art reference disclosure of each and every element of

the claimed invention arranged in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 U.S.P.Q. 481 (Fed. Cir. 1984). In addition, the allegedly anticipating reference must be enabling and describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art. *In re Paulsen, supra*, at 1673. The anticipation determination is viewed from one of ordinary skill in the art. There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

Bonaventure fails to disclose or suggest at least the following elements of claim 1: (i) selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes and (ii) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression.

Bonaventure discusses nuclei and subnuclei gene expression profiling in mammalian brain. Gene expression profiles were measured from seven different laser-captured brain nuclei or subnuclei in three adult rats (Fig. 2a). Genes were considered expressed if the difference to the background was significant. The author presented data on the number of genes that are enriched in one nucleus with respect to all the six other nuclei (see Table 1). Pair-wise scatter plots were used to determine correlation between different nuclei. At the bottom of column 2 on page 46, Bonaventure indicates that their hierarchical cluster analysis demonstrated that each of the seven nuclei had a unique gene expression profile and that there was a molecular basis for the previously defined anatomic nuclei or subnuclei.

The Bonaventure reference is concerned with gene expression profiling. The authors evaluated expression among brains of different individuals with the purpose of understanding aspects of brain biology. As can be seen, Bonaventure is concerned with individual nuclei and their respective gene expression profiles and not with determining a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes. As indicated by the author on page 40, paragraph 2.6, a full collection of cDNA clones was present on the chip. Furthermore, while Bonaventure states that the highest

number of enriched genes for each criterion was found in LC, there is no disclosure or suggestion in the reference of selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression. As mentioned above, anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention arranged in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, *supra*.

Claims 2-4 are patentable over Bonaventure at least as a result of their respective dependency from claim 1, which, as demonstrated above, is patentable over the teaching of Bonaventure.

With respect to claim 6, the Office Action contends that Bonaventure carries out a plurality of differential gene expression experiments using a plurality of experimental sets and using a plurality of cellular nuclei (referring to Table 1 of the reference).

Claim 6 is directed to the method of claim 1 wherein the nucleic acid sample pairs are tissue pairs. The Bonaventure reference does not disclose or suggest such a method. The experiments represented in Table 1 are gene expression profiling measurements from seven different brain nuclei or subnuclei in three adult rats. There is no disclosure or suggestion of tissue pairs.

With respect to claims 7-8, the Office Action argues that Bonaventure discloses that each sample is hybridized to a separate substrate, as in claim 8, and, in the process of being hybridized to separate substrates they are being hybridized to a substrate, as in claim 7.

Applicant respectfully traverses this ground of rejection. Claim 7 is directed to a method of claim 1 wherein in step (a) the differential expression experiments are conducted by contacting a nucleic acid sample pair with a substrate having nucleic acid probes immobilized thereon. The Bonaventure reference is concerned with gene expression profiling. The authors are concerned with expression among brains of different individuals with the purpose of understanding aspects of brain biology.

For reasons similar to those discussed above for the inappropriateness of the rejection of claim 7 as anticipated by Bonaventure, claim 8 is patentable over the reference.

Claims 1-8 and 20-26 were rejected under 35 U.S.C. 102(e) as being anticipated by Collins, *et al.* (U.S. Patent Publication No. 2004/0101846) (Collins).

The Office Action asserts that, with respect to claim 1, Collins discloses selection of nucleic acid sample pairs by hybridizing nucleic acid sample pairs to nucleic acids on microarrays and selecting for those sample pairs that maximize the number of mRNA's that are differentially expressed (referring to paragraph 70, lines 1-8).

The cited passage from the reference discusses a representative example of the empirical evaluation step of the methods disclosed in the reference. Multiple copies of a microarray that includes candidate 60-mer probes having sequences identified by the prior sequence identification step were produced using an *in situ* nucleic acid array synthesis protocol. These resultant microarrays were then hybridized to 10 different tissue/cell line combinations (4 replicates per sample pair): one self-vs.-self and 9 sample pairs chosen to maximize the number of mRNA's that are differentially expressed between the members of the pair.

It is readily seen from the context of the above passage (see paragraphs 0048, *et seq.*) that Collins is discussing a method for identifying candidate probes for a target nucleic acid and not with determining combinations of nucleic acid sample pairs. At paragraph 48, Collins indicates that his invention provides methods of identifying a sequence of a nucleic acid that is suitable for use as a surface immobilized probe for a target nucleic acid.

Collins fails to disclose or suggest at least the following elements of claim 1: (i) selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes and (ii) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression.

Collins discloses no more than what is discussed in the background section of the present application. At the bottom of page 3 to the middle of page 4, the specification indicates that an important step in designing arrays is the selection of a specific probe or mixture of probes that may be used in the array. One difficulty in the design of oligonucleotide arrays is that oligonucleotides targeted to different regions of the same gene can show large differences in hybridization efficiency. The

specification discusses one approach to validating probes wherein candidate probe sequences are evaluated for their performance under a plurality of different experimental sets. A plurality of differential gene expression experiments are conducted to obtain a collection of empirically obtained performance data values for each of the candidate nucleic acid probe sequences for each of the plurality of different experimental conditions. Such an approach utilizes tissue pair combinations. Further in the present specification at the bottom of page 7, Applicant indicates that the present invention may be employed for selecting an optimal nucleic acid sample pair combination such as a tissue pair combination for validating probes for their use in analyses involving differential gene expression.

The present invention can be employed for identifying nucleic acid sample pair combinations such as tissue pair combinations that can be employed in the methods of Collins. As discussed in the present specification (page 21, lines 2-13), in methods of identifying a sequence of a nucleic acid that is suitable for use as a surface immobilized probe for a target nucleic acid, it is desirable to have a sample pair combination with maximized diversity so that the sample pair combination has the greatest diversity with respect to genes differentially expressed. Embodiments of the present invention assist in avoiding the selection of nucleic acid sample pairs that have redundant genes considered differentially expressed. Furthermore, as also discussed in Applicant's specification, embodiments of the invention may be employed to decrease the number of nucleic acid sample pairs employed in the combination.

Claims 2-8 are patentable over Collins at least as a result of their respective dependency from claim 1, which, as demonstrated above, is patentable over the teaching of Bonaventure.

With respect to claim 20, the Office Action alleges that Collins discloses evaluating candidate probes using sample pairs identified through the method of claim 1 (referring to paragraph 69).

As demonstrated above, Collins does not disclose or suggest the method of claim 1, i.e., a method for selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes. Therefore, claim 20 is patentable over Collins at least by virtue of its dependency from claim 1.

Claims 21-26 are patentable over Collins for reasons similar to those discussed above with respect to the patentability of claims 1 and 20 over Collins.

Rejection under 35 U.S.C. §103

Claims 20-24 and 26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaventure, as applied to claims 1-4 and 6-8 above, and further in view of Dooley, *et al.* (U.S. Patent Publication No. 2001/0046671) (Dooley).

Applicant acknowledges the recognition in the Office Action that Dooley does not disclose using a sample pair from claim 1. However, the Office Action alleges that Bonaventure discloses obtaining a sample pair by a method of claim 1. The Office Action asserts that it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to modify the method of Bonaventure to use it in combination with the method of Dooley to prepare probes that are specific for the tissue pair of Bonaventure. One of ordinary skill in the art, contends the Office Action, would have been motivated to do this because, as suggested by Dooley, by designing an "informative array," Bonaventure would be more likely to identify differentially expressed genes (referring to paragraph 19, lines 4-8).

Without acquiescing in the assertions in the Office Action regarding the disclosure of Dooley, Bonaventure, as demonstrated above, does not disclose or suggest a method as claimed in claim 1. Therefore, even if the combination of teachings of the references were made as asserted in the Office Action, one still would not be in possession of the presently claimed methods of claims 20-24 and 26. Dooley does not cure the deficiencies of Bonaventure. The combined teachings of Bonaventure and Dooley do not disclose or suggest at least the following elements of claim 1: (i) selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes and (ii) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression.

In order to maintain a rejection under 35 U.S.C. §103 an examiner must first establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Piasecki*, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984). In determining the propriety of the Patent Office case for obviousness in the

first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification. *In re Lintner*, 458 F.2d 1013, 173 U.S.P.Q. 560 (C.C.P.A. 1972). Hindsight reconstruction using the disclosure and claims in prosecution as a guide to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention is not permitted. *In re Fine*, *supra*.

Bonaventure and Dooley, either individually or in combination, do not disclose or suggest the method of claim 1. Accordingly, substituting the teaching of Bonaventure in that of Dooley does not result in the methods claimed in instant claims 20-24 and 26. No *prima facie* case of obviousness has been established.

Double Patenting

Claims 20-22 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 18-19 of copending application U.S. Serial No. 10/303,160 (the '160 application). It should be noted that the '160 application and Collins above are one and the same. The Office Action asserts that the rejection is a vogel type, i.e. a genus makes species obvious if species are specifically disclosed in that copending application.

Claim 1 of the '160 application is directed to a method of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized probe for a target nucleic acid. The method comprises: (a) identifying a plurality of candidate probe sequences for the target nucleic acid based on at least one selection criterion; (b) empirically evaluating each of the candidate probe sequences under a plurality of different experimental sets to obtain a collection of empirical data values for each of the candidate nucleic acid probe sequences for each of the plurality of different experimental sets; (c) clustering the candidate probe sequences into one or more groups of candidate probe sequences based on each candidate probe sequence's collection of empirical data values, wherein each of the one or more groups exhibits substantially the same performance across the plurality of experimental sets; (d) selecting one of the one or more groups based on at least one criterion; and (e) choosing a candidate probe sequence from the selected group to as the sequence of the nucleic acid that is suitable for use as a substrate immobilized probe for the target nucleic acid. It is readily seen from claim 1 of the

'160 application that what is disclosed is a method for identifying candidate probes for a target nucleic acid.

As indicated in M.P.E.P. section 804, a double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103 except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 1 of the '160 application does not disclose or suggest at least the following elements of claims 20-22, which each depend respectively from claim 1 of the present application: (i) selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes and (ii) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression.

Furthermore, the Office Action states that the "empirical evaluation" step of claim 1 of the '160 application is generic to the empirical evaluation employing a nucleic acid sample pair selected by a method according to present claim 1, from which present claim 21 depends. On page 12, the Office Action states that a genus makes a species obvious if species are specifically disclose in that copending application (referring to the '160 application). Thus, even if for the sake of argument one were to accept the above proposition, the rejection of claim 21 must fail because the '160 application, as recognized in the Office Action, does not disclose species as required in the vogel type rejection. As the Office Action states, the "empirical evaluation" step of claim 1 of the '160 application is generic to the "empirical evaluation employing a nucleic acid sample pair selected by a method according to present claim 1, from which present claim 21 depends.

At the top of page 14, the Office Action asserts that the portion of the specification of the '160 application that supports the recited "empirical evaluation" procedure includes an embodiment that would anticipate the empirical evaluation employing a nucleic acid sample pair step of the instant claim 21. The Office Action

contends that paragraph 70, lines 6-10, of the '160 application specifically disclose an empirical evaluation wherein the empirical evaluation employs a nucleic acid sample pair selected by a method of instant claim 1.

Applicant disagrees. As discussed above with regard to the rejection of claim 1 over Collins, the above-cited passage from the reference discusses a representative example of the empirical evaluation step of the methods disclosed in Collins. Multiple copies of a microarray that includes candidate 60-mer probes having sequences identified by the prior sequence identification step were produced using an *in situ* nucleic acid array synthesis protocol. These resultant microarrays were then hybridized to 10 different tissue/cell line combinations (4 replicates per sample pair): one self-vs.-self and 9 sample pairs chosen to maximize the number of mRNA's that are differentially expressed between the members of the pair.

It is readily seen from the context of the above passage (see paragraphs 0048, *et seq.* of the reference) that Collins is discussing a method for identifying candidate probes for a target nucleic acid. At paragraph 48, Collins indicates that his invention provides methods of identifying a sequence of a nucleic acid that is suitable for use as a surface immobilized probe for a target nucleic acid. There is no disclosure or suggestion of at least the following elements of claims 20-22, which each depend respectively from claim 1 of the present application: (i) selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes and (ii) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression.

Claims 20 and 22 are not disclosed or suggested by claims 1 and 18-19 of the '160 application for reasons similar to those discussed above with regard to the rejection of claim 21.

In paragraph 10 on page 15, the Office Action contends that the '160 application would form the basis for a rejection of claims 20-22 under 35 U.S.C. 103(a) if the commonly assigned application qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention of the present application was made.

As demonstrated above, the '160 application (also referred to as Collins above) does not disclose or suggest at least the following elements of claims 20-22, which each depend respectively from claim 1 of the present application: (i) selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes and (ii) selecting a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression.

Conclusion

Claims 1-11 and 20-26 satisfy the requirements of 35 U.S.C. §§112, 102 and 103. Furthermore, there is no obviousness-type double patenting between claims 1 and 18-19 of the '160 patent application and present claims 20-22, nor are claims 20-22 disclosed or suggested by the disclosure of the '160 application (otherwise known as Collins). Allowance of the above-identified patent application, it is submitted, is in order.

Respectfully submitted,

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